Biomedicine & Pharmacotherapy 93 (2017) 1116–1127

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Dissolving microneedles for transdermal drug delivery: Advances and challenges

Kevin Ita

College of Pharmacy Touro University, Mare Island-Vallejo, California, CA, 94592, USA

ARTICLE INFO

Article history:
Received 16 May 2017
Received in revised form 4 July 2017
Accepted 5 July 2017

Keywords:
Dissolving microneedles
Transdermal
Drug delivery
Polymers
Skin
Polyvinylpyrrolidone
Maltose
Micromolding

ABSTRACT

Over the last number of years, a significant body of evidence has shown the benefit of using dissolving microneedles (DMNs) for transdermal drug delivery. These devices are prepared from a wide range of materials such as sugars and polymers. DMNs are mainly fabricated by micromolding, photopolymerization, drawing lithography and droplet-airborne blowing. In this review, we have focused on the advances made in the field in recent years using a representative set of studies. Although the list of studies is not exhaustive, they highlight the challenges encountered such as the need to increase mechanical strength as well as medication dose while ensuring fast release of the active ingredient. DMNs can be used to delivery low molecular drugs as well as peptides, proteins and other high molecular weight compounds.

Contents

1. Introduction

The transdermal route of drug administration combines the advantages of oral drug delivery such as convenience with the avoidance of presystemic metabolism observed with parenteral drug delivery [1]. However, the stratum corneum, which is the outermost layer of the skin, prevents drugs and other compounds from easily entering the systemic circulation [2]. The elegant architecture of the stratum corneum made from corneocytes and intercellular lipid matrix is thought to be responsible for this 'brick and mortar' structure and the tremendous barrier function [3]. There are several ways to overcome this barrier including the use of iontophoresis [4], chemical penetration enhancers [5], sonophoresis [6], prodrugs [7] and microneedles [8–10].

E-mail address: kevin.ita@tu.edu (K. Ita).

http://dx.doi.org/10.1016/j.biopha.2017.07.019
0753-3322/

Microneedles are arrays of ultra-small needles typically with lengths in the micrometer range (less than 1000 micrometers) which create pores and enable medications to be delivered locally in the skin or across the skin into the systemic circulation [11–13]. Unlike regular hypodermic needles, MNs create micro-dimensional and painless pathways [14]. MNs can lead to improved patient compliance with medication regimen as they do not stimulate nerves that are associated with pain and patients with needle phobia are more likely to use microneedles because of the painlessness and minimal invasiveness [11]. There are five types of microneedles- solid [15,16], coated [17], hollow [18], hydrogel-forming [19] and dissolving [20–22]. Four types(solid, coated, hollow, dissolving) are shown in Fig. 1 [23] and the differences between dissolving and hydrogel-forming microneedles [22] are shown in Fig. 2.

Solid microneedles are usually made from different types of metals including stainless steel [24,25], silicon [26] and titanium [27]. Laser micromachining is a widely used method for the fabrication of these microneedles [28]. Coated microneedles release medications upon insertion into the skin [29]. Recently, solid metal microneedles coated with influenza virus-like particle (VLP) vaccine were inserted into skin for intradermal immunization [29]. A limitation of the coated microneedle technique is that such microneedles leave behind sharp, biohazardous waste after use, which may pose safety concerns and require special disposal needs [30]. Dissolving microneedles (DMs) (Fig. 3) do not leave harmful materials in the skin and do not generate sharp needle waste [31]. Another advantage of DMNs is that the use of this drug delivery system is based on a one-step application process which is convenient for patients [11]. When using solid microneedles, pores are first created in the skin and then the patch is applied [16]. Solid microneedles merely make micropores in the skin. After micropores are formed, a sponge containing a drug solution or cream is applied onto the skin [32].

The pre-treatment of the human skin using silicon or metal MN can in itself be problematic, because the biocompatibility of silicon is still questionable and broken silicon or metal microneedles could be harmful to the skin [33]. The taxonomy of microneedles has somewhat changed over the last few years to include hydrogel-forming microneedles. Hydrogel-forming microneedles are prepared from polymeric materials that either dissolve rapidly in the skin interstitial fluid following insertion to deliver a drug payload, or swell in the skin, forming continuous conduits between drug reservoirs and the viable skin [19]. Microneedles prepared from aqueous blends of 20% w/w poly(methylvinylether/maelic acid) and crosslinked with glycerol by esterification tend to form hydrogels upon insertion into the skin [33]. Hollow microneedles require a reservoir into which the drug solution is placed [32]. Interestingly, peptide/protein drugs often have a problem of stability in such an aqueous environment [32]. In contrast, the release of medications from dissolving MNs is based on the "poke and release" principle [23]. This means that DMNs first create pores in the skin and then release the drug into those holes [23,34].

DMs are made from water-soluble materials as maltose, polyvinylpyrrolidone, chondroitin sulfate, dextran, hyaluronic acid, and albumin, from which drug molecules are delivered into the skin merely by pushing DM onto the skin with a finger [12,30,32,35,36]. Because they are made from biocompatible and water-soluble materials, such as cellulose derivatives and sugars, they dissolve completely in the skin and thereby leave behind no biohazardous sharps tips after use [21]. DMs usually soften and dissolve within biological tissues upon penetration thereby preventing damage due to the mechanical forces associated with application [35]. As a result, dissolving microneedles are more advantageous in comparison with silicon and metal needles. Silicon and metal microneedles are capable of breaking *in vivo* [37]. DMs are also useful because they are designed to deliver a variety of drugs, are easy to use and are inexpensive [30]. More importantly, these devices can be self-administered without medical training [21] which is crucial especially for developing countries. The materials used for the fabrication of dissolving microneedles are cost-effective, widely available, and can be used without harsh processing conditions such as high temperatures [38].

But DMs also have disadvantages. Lau and coworkers noted that the tips and pedestals of dissolving microneedles have different mechanical performance requirements [37]. The tips need adequate mechanical robustness to create cavities in the stratum corneum. On the other hand, the pedestal enables flexible adhesion to skin and can transmit the force to the tips [37]. Chu et al. have also pointed out that it can be difficult to control the dose encapsulated and delivered from dissolving microneedles due in part to drug diffusion within the water-soluble microneedle matrix during fabrication [30].

It has been emphasized in the scientific literature that DMs typically have low mechanical strength which prevents consistent

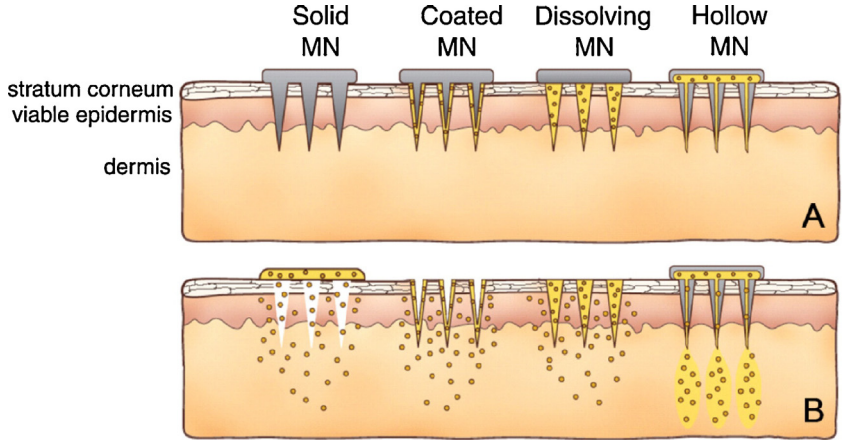

Fig. 1. Transdermal drug delivery with different microneedles. Microneedles are first applied to the skin (A) and then used for drug delivery (B). The skin is pretreated with solid microneedles and then the drug diffuses through the pores in the skin from a topical drug delivery system (solid MN). After insertion of drug-coated microneedles into the skin, the drug coating dissolves in the skin (coated MN). Dissolving microneedles are arrays of ultra-small needles made from water-soluble materials typically with lengths in the micrometer range (less than 1000 μm). They create pores in the skin and release drug payload upon microneedle dissolution (dissolving MN). Hollow microneedles are like conventional needles but shorter (less than 1000 μm) and are used to inject liquid formulations into the skin (hollow MN).
(Reproduced with permission from reference 23)